REMARKS

Claims 16-25 are pending. No claims have been allowed. Claims 16-19, 24, and 25 have been amended in the manner suggested by the Examiner.

There appears to be a misunderstanding as to what the applicant's vaccine is. The paragraph bridging columns 2 and 3 disclose the vaccine that is claimed. Example 1 discloses the method for making the claimed vaccine. In step 6, the supernatant fraction containing all of the extractable intracellular proteins was mixed with the liquid phase containing extracellular proteins. In step 7, an aliquot of the mixture was analyzed by SDS gel electrophoresis to confirm that the mixture contained the three immunodominant proteins contributed by the supernatant fraction containing all of the extractable intracellular proteins. In some cases, the immunodominant proteins were cut from the gel and added to Mendoza's original vaccine (SCAV). In step 8, after visualizing the immunodominant proteins on the gel, the remainder of the mixture was precipitated with acetone and in step 9, the precipitate was resuspended in water. In step 10, the resuspended precipitate was dialyzed against water and then stored until use. The vaccine in step 10 contains all of the extractable intracellular proteins including the three immunodominant proteins and the extracellular proteins. Thus, Example 1 discloses

the method for making the vaccine in the claims.

Example 2 provides results from a vaccination therapy experiment where horses were vaccinated with the vaccine prepared as in Example 1 (page 8, lines 13-21). While the example appears to discuss the results for Mendoza's original vaccine containing the three immunodominant proteins, the Example is really discussing the results for the vaccine prepared as in Example 1. Thus, Example 2 demonstrates that the vaccine of the claims was efficacious in the same manner as Mendoza's original vaccine (SCAV) containing the three immunodominant proteins purified by gel electrophoresis as mentioned in step 7 and as disclosed in Mendoza (1995) and Mendoza (1996). Example 4 discloses that the vaccine of Example 1 was able to cure a human chronically infected with *Pythium insidiosum*.

In light of the above, the applicant's vaccine in the claims is supported by the specification and is clearly distinguishable from the vaccine disclosed in Mendoza (1995) and Mendoza (1996).

1. Claim 25 was objected to for omitting a modifier between precipitated and acetone.

The omission has been corrected.

2. Claims 16-19 and 24 were rejected under 35 U.S.C. §

112, second paragraph.

Claims 16, 17, 18, 19, and 24 have been amended in the manner suggested by the Examiner.

3. Claims 16-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mendoza *et al.* (1996), Mendoza *et al.* (1992a) (IDS: AI), Mendoza *et al.* (1992b) (IDS: AJ), Sigma Catalogue (1992), Amicon Catalogue (1993), and Mendoza abstract (1995).

The applicant believes that the prior art does not render the instant invention obvious for the following reasons.

The applicant's vaccine as disclosed in the instant application provides a result that one with ordinary skill in the art would not expect by merely combining the intracellular proteins from the CMV and the extracellular proteins of the SCAV. As taught by Mendoza (1992a), neither the CMV nor the SCAV is able to cure chronically infected horses. Thus, one with ordinary skill in the art would have no reason to believe that a vaccine that combined all of the extractable intracellular proteins with extracellular proteins as taught by the applicant in the instant application would produce a vaccine with curative properties not seen with either the vaccine consisting solely of intracellular proteins (CMV) or extracellular

proteins (SCAV). The ability of the applicant's vaccine as disclosed in the instant application to cure chronically infected horses would not have been unexpected.

While Mendoza (1992b) discloses that antisera from a horse with pythiosis reacted with 32K, 30K, and 28K immunodominant proteins from *Pythium insidiosum*, and Mendoza (1995) and Mendoza (1996) both describe a vaccine which consisted of the SCAV with the addition of the three immunodominant proteins and which was able to cure chronically infected horses, the prior art provides no motivation to one with ordinary skill in the art to make a vaccine that combined *all* of the extractable intracellular proteins with the extracellular proteins. It is true that the three immunodominant proteins are intracellular proteins; however, while the prior art taken as a whole suggests that a vaccine which contained extracellular proteins with the three immunodominant proteins could be efficacious, the prior art also suggests that a vaccine consisting of all of the extractable intracellular proteins added to the SCAV would not produce the same result. That is because the CMV, which *inter alia* contained the three immunodominant proteins, was unable to cure chronically infected horses. The inability of the CMV to cure chronically infected horses would suggest that the total population

of intracellular proteins contained other constituents that interfered with the ability of the three immunodominant proteins to cure chronically infected horses. Therefore, to make a vaccine to cure chronically infected horses, one with ordinary skill in the art would have followed the teachings of Mendoza (1995) and Mendoza (1996) and prepared a vaccine by adding only the three immunodominant proteins to the SCAV, not by mixing all of the extractable intracellular proteins with the extracellular proteins as taught by the applicant in the instant application.

In light of the above, the Sigma Catalogue (1992) and the Amicon Catalogue (1993) in view of the above of the prior art would not have made the applicant's invention obvious. Neither catalogue contains any disclosure which would have made preparing a vaccine consisting of all of the extractable intracellular proteins with the extracellular proteins suddenly obvious when viewed in light of the above prior art.

Because the applicant's vaccine had the unexpected ability to cure chronically infected horses in light of the prior art which showed that a vaccine containing the all of the extractable intracellular proteins lacked that ability whereas a vaccine containing the three particular immunodominant proteins,

which had been purified and mixed with extracellular proteins, could cure chronically infected horses, the rejection appears to be a hindsight rejection based on the applicant's disclosure. Without the applicant's disclosure in the instant application, there would have been no reason for one skilled in the art to expect that a vaccine that contained all of the extractable intracellular proteins mixed with the extracellular proteins would cure chronically infected horses. Thus, one with ordinary skill in the art would not have been motivated to prepare a vaccine as taught by the applicant in the instant application.

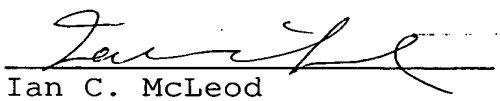
Furthermore, the prior art does not even remotely suggest the use of the claimed vaccine in humans. Because humans and horses are not evolutionarily related, it is unlikely that one of ordinary skill in the art would have considered a veterinary vaccine for use in humans. Therefore, Claims 16 and 17, which specifically call for a method for vaccinating humans, would not have been obvious over the prior art.

In light of the above, Claims 16-25 are not obvious over the prior art. Reconsideration of the rejection is requested.

Claims 16, 17, 18, 19, 24, and 25 have been amended to place the claims in proper form for

allowance. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attachment is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**." Notice of Allowance is requested.

Respectfully,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 16, 17, 18, 19, 24, and 25 have been amended as follows.

-16-(Fourth amended)

A method for treatment of Pythiosis in human patients having the [disease] Pythiosis which comprises:

(a) providing a vaccine containing a mixture of mixed intracellular proteins and mixed extracellular proteins of *Pythium insidiosum* in a sterile aqueous solution, wherein the mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of the *Pythium insidiosum* grown in a culture medium, and the mixed extracellular proteins, which consist essentially of proteins removed from the culture medium for growing the *Pythium insidiosum*, are in water and the mixture has been dialyzed to remove low molecular weight components less than 10,000 MW; and

(b) vaccinating the patient with the vaccine.

-17-(Amended)

The method of Claim 16 wherein [the vaccination is subcutaneous] vaccinating the patient with the vaccine is subcutaneous.

-18-(Fourth amended)

A method for the treatment of Pythiosis in a mammal having the [disease] Pythiosis which comprises:

(a) providing an injectable vaccine derived from growing cells of *Pythium insidiosum* in a culture medium which comprises in a sterile aqueous solution in admixture:

(1) mixed intracellular proteins, which consist essentially of proteins removed from disrupted cells of the *Pythium insidiosum* separated from the culture medium; and

(2) mixed extracellular proteins, which consist essentially of proteins removed from the culture medium separated from the cells of the *Pythium insidiosum*;

wherein the admixture in water has been dialyzed to remove low molecular weight components less than 10,000 MW to produce the vaccine; and

(b) vaccinating the mammal with the vaccine.

-19-(Fourth amended)

The method of Claim 18 wherein the removed proteins in the admixture have been provided by growing cells of the *Pythium insidiosum* in the culture medium, then killing the cells, then separating the killed cells from the culture medium to produce a first supernatant to provide the mixed extracellular proteins of (a)(2) and then disrupting the killed cells in sterile water and removing the disrupted cells <u>from the sterile water containing the mixed intracellular proteins</u> to provide the mixed intracellular proteins of (a)(1) in a second supernatant, combining the first and second supernatants, precipitating the proteins, resuspending the precipitated proteins in sterile water, and dialyzing the resuspended proteins in sterile water to remove the material less than 10,000 MW.

-24-(Fourth amended)

The method of Claim 19 wherein the disrupted cells are removed from the <u>sterile water containing the</u> mixed intracellular proteins by centrifugation to provide the mixed intracellular proteins of (a)(1) in the second supernatant.

The method of Claim 19 wherein the mixed intracellular and extracellular proteins from (a)(1) and (a)(2) are precipitated with acetone to produce a precipitate and resuspending the precipitate in sterile distilled water for the dialysis.